UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: EPA Reg. # : 67071-R

TO: John Lee; PM 31; Attn: Valdis Goncarovs
Antimicrobial Program Branch
Registration Division (70505H)

FROM: David L. Ritter, Toxicologist
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)
DLR 10-19-94

THRU:: Tina E. Levine
~~Thomas C. Ellwanger~~, Jr., Section Head
Precautionary Review Section
Registration Support Branch
Registration Division (7505W)
Tina E. Levine
12/14/94

Registrant: Thor Americas, Inc.
37 North Ave.
Norwalk, CT 06851

FORMULATION FROM LABEL:

Active Ingredient(s):	% by Wt.
5-chloro-2-methyl-4-isothiazolin-3-one...	1.1%
2-methyl-4-isothiazolin-3-one.....	0.4%
Inert Ingredient(s):	98.5%
Total	100.0%

Action Requested:

1. Review acute toxicity studies.

2. Review Precautionary Labeling.

PRS Response:

1. The studies have been reviewed and DERs are attached.

   The eye irritation study was placed in TOX Category I because of severe corneal/conjunctival injury in a single rabbit assay. The study was classified CORE Guideline.

2

The acute oral and inhalation studies were placed in TOX Category IV because LD_{50} and LC_{50} exceeded those required for a limit test.

The acute dermal study was placed in TOX Category III because no deaths were reported in a 2000 mg/kg limit test.

The dermal irritation study was not categorized because the animals were only followed for 14 days while there was yet injury. It has been classified as CORE Supplementary.

The product is a rather strong dermal sensitizing agent and the study was classified CORE Guideline in a Guinea Pig Maximization Test.

This report included data from historical studies using formalin as the positive control agent. The studies demonstrate that the test system will detect dermal sensitizing agents.

The data reviewed in support of this registration are summarized here:

Acute Toxicity Data Requirements (40 CFR §158.340). Pesticide Assessment Guidelines, Subdivision F. Hazard Evaluation: Human and Domestic Animals. (1982; revised 1984).

Data Required	MRID #	Toxicity Category	Classification
Acute Oral (§81-1)	427465-11	IV	G
Acute Dermal (§81-2)	" -12	III	G
Acute Inhal. (§81-3)	" -13	IV	G
Eye Irr. (§81-4)	" -14	I	G
Dermal Irr. (§81-5)	" -15	--	S
Dermal Sens. (§81-6)	" -16	Sens.	G

A dermal irritation study is required to complete the data base for this product.

Precautionary Labeling reivew:

1. Signal Word: Acceptable (Danger!)

2. Precautionary Statements:

Replace the present statement with the following:

"Corrosive. Causes irreversible eye damage. Due to corrosive nature, may be harmful or fatal if swallowed. Harmful if absorbed through skin. Do not get in eyes, on skin or on clothing. Wear goggles, face shield or safety glasses. Wash thoroughly with soap and water after handling. Remove

contaminated clothing and wash before reuse."

3. Add the following statement to the precautionary statements:

"Prolonged or frequent repeated skin contact may cause allergic reactions in some individuals".

4. Statement of Practical Treatment:

Revise as follows:

IF IN EYES: Flush with water for 15 minutes. Call a physician.

IF SWALLOWED: Drink promptly a large quantity of milk, egg whites, gelatin solution, or if these are not available, drink large quantities of water. Avoid alcohol.

IF ON SKIN: Wash with plenty of soap and water. Get medical attention.

5. Add the following "Note To Physician" below the statement of practical treatment:

NOTE TO PHYSICIAN: Probable mucosal damage may contraindicate the use of gastric lavage.

6. The product meets the criterion for restricted use based on Category I eye toxicity. The Product Manager must decide if alternative labeling exists which will offset the hazard.

7. CRP is not required for this product because the use patterns do not appear to reflect residential use.

4

DATA EVALUATION RECORD FOR ACUTE ORAL TOXICITY TESTING §81-1

Product Manager (PM): 31 EPA Reg. No.: ~~67-71~~ 67071-R

Reviewer: David L. Ritter, Toxicologist DLR 10-19-94

MRID No.:427465-11

Testing Laboratory: Huntingdon Research Centre Ltd.,
PO Box 2, Huntingdon
Cambridgeshire PE18 6ES England

Title Of Report: Acute Oral Toxicity to the Rat of Acticide LG

Date of Report: 5/8/91

Lab. No.: 9181D/THR 11/AC

Author(s): Paul Baldrick

Species: Sprague Dawley rats Sex: 5M + 5F/grp Wt.: 114 - 137 gm

Source: Charles River U.K. Limited, Margate, Kent, England

Test Material: Acticide LG undiluted

Quality Assurance (40 CFR, Section 160.12): Acceptable

Summary:

LD_{50} Males = 5.7 gm/kg; Females = 5.2 mg/kg

Toxicity Category: IV CORE Classification: Guideline

Procedure (Deviation From Series 81-1):

Standard laboratory animal husbandry and GLP were observed.

Animals were weighed initially, on day 8 and at termination.

Test Article Administration:

Test Article was administered once by gavage to groups of 5M + 5F at doses of 3.2, 5.0 and 8.0 gm/kg.

Animals were observed initially several times during day one, then daily thereafter for fourteen days for mortality and signs of toxicity.

Animals dying during the observation period and those surviving to termination were subjected to gross necropsy.

Results:

All surviving animals gained weight approximately normally.

REPORTED MORTALITY

DOSAGE MG/KG	MALES No.Dead/No. Exposed	FEMALES No. Dead/No. Exposed	COMBINED No. Dead/No. Exposed
3.2 gm/kg	0/5	0/5	0/10
5.0 gm/kg	1/5	2/5	3/10
8.0 gm/kg	5/5	5/5	10/10

LD_{50} Males = 5.7 gm/kg; Females = 5.2 mg/kg

Post mortem examination was unrevealing of effect.

Conclusion(s):

Toxicity Category: IV CORE Classification: Guideline

6

DATA EVALUATION RECORD FOR DERMAL TOXICITY TESTING §81-2

Product Manager (PM): 31 EPA Reg. No.: 67071-R

Reviewer: David L. Ritter, Toxicologist DLR 10-19-94

MRID No.:427465-12

Testing Laboratory: Huntingdon Research Centre Ltd.,
PO Box 2, Huntingdon
Cambridgeshire PE18 6ES England

Title Of Report: Acute Dermal Toxicity to the Rat of Acticide LG

Date of Report: 5/8/91

Lab. No.: 9182D/THR 12/AC

Author(s): Paul Baldrick

Species: Sprague Dawley rats Sex: 5M + 5F/grp Wt.: 229 - 250 gm

Source: Charles River U.K. Limited, Margate, Kent, England

Test Material: Acticide LG undiluted

Quality Assurance (40 CFR, Section 160.12): Acceptable

Summary:

LD_{50} Males > 2000 mg/kg; LD_{50} Females > 2000 mg/kg

Toxicity Category: III CORE Classification: Guideline

Procedure (Deviation From Series 81-2):

Standard laboratory animal husbandry and GLP were observed.

Animals were weighed initially, and on days 8 and 15.

Animals were clipped free of dorsal hair 24 hours prior to application. 2000 mg/kg undiluted Test Article was applied topically under a gauze patch to an area of approximately 50 mm x 50 mm which was secured with an impermeable dressing.

After 24 hours the dressings were removed and the test sites cleansed with water.

Animals were observed for effects at "frequent intervals on the day of dosing, then twice daily thereafter for 14 days.

Animals dying during the observation period and those surviving to termination were subjected to gross necropsy.

Results:

Animals gained weight normally.

There was no mortality.

REPORTED MORTALITY

DOSAGE MG/KG	MALES No.Dead/No. Exposed	FEMALES No. Dead/No. Exposed	COMBINED No. Dead/No. Exposed
2000 mg/kg	0/5	0/5	0/10

Conclusions:

LD_{50} Males > 2000 mg/kg; LD_{50} Females > 2000 mg/kg

Toxicity Category: III CORE Classification: Guideline

DATA EVALUATION RECORD FOR ACUTE INHALATION TOXICITY TESTING § 81-3

Product Manager (PM): 31 EPA Reg. No.: 67071-R

Reviewer: David L. Ritter, Toxicologist DLR 10-19-94

MRID No.:427465-13

Testing Laboratory: Huntingdon Research Centre Ltd.,
PO Box 2, Huntingdon
Cambridgeshire PE18 6ES England

Title Of Report: Acticide LG: Acute Inhalation Toxicity in Rats, 4 Hour Exposure.

Date of Report: 4/24/94

Lab. No.: THR 10/911109

Author(s): Graham C. Jackson & Colin J. Hardy

Species: Sprague Dawley rats Sex: 5M + 5F/grp Wt.: ca. 200 gm

Source: Charles River U.K. Limited, Margate, Kent, England

Test Material: Acticide LG undiluted

Dosage: See under "Results" below.

Quality Assurance (40 CFR, Section 160.12): Acceptable

Summary:

Toxicity Category: IV Classification: Guideline

Procedure (Deviation From Series §81-3:

Standard laboratory animal husbandry and GLP were observed.

Animals were weighed daily.

Feed and water consumption was measured.

Animals dying during the observation period and those surviving to termination were subjected to gross necropsy. Lung to body weight ratios were determined in all rats.

Generation of Test Aerosol:

Undiluted Test Article was injected by syringe and pump to an unidentified aerosol generator. Dosage was varied by varying the pump flow rates.

Measurement of Test Aerosol:

Analytical Concentration: 5 air samples per exposure level were taken through an absorption trap and concentration of the component AIs were measured using HPLC.

Particle Size Distribution: 2 air samples at ca. 1.5 and 3.5 hours were taken from each exposure atmosphere using a Marple/Andersen cascade impactor. Each stage was eluted with methanol and analyzed using HPLC.

5M + 5F/group were exposed to aerosols containing 0.0, 1.53, 2.05, 2.83 and 4.49 mg/l for a duration of 4 hours. Survivors were returned to their cages.

Results:

A modest initial weight reduction was reported for all survivors. Animals dying during the study lost weight.

Signs of toxicity included wetness about the eyes, snout and mouth; exaggerated respiration and death.

Particle size determination was expressed in terms of the component Ais and not in terms of the formulation *per se**.

Dose mg/l	MMAD ± δg		% > 4μm	
	MIT	CIT	MIT	CIT
1.53	1.9 ± 2.5	0.7 ± 4.3	82%	87%
2.05	1.8 ± 2.1	1.3 ± 3.3	90%	84%
2.83	2.4 ± 2.1	1.8 ± 2.4	57%	68%
4.49	2.0 ± 2.1	1.8 ± 2.3	68%	67%

REPORTED MORTALITY

DOSAGE MG/Liter	MALES No.Dead/No. Exposed	FEMALES No. Dead/No. Exposed	COMBINED No. Dead/No. Exposed
1.53	2/5	0/5	2/10
2.05	1/5	0/5	1/10
2.83	3/5	1/5	4/10
4.49	5/5	4/5	9/10

* MIT = 2-methyl-4-isothiazolin-3-one

10

CIT = 5-chloro-2-methyl-4-isothiazolin-3-one

Feed and water consumption were generally affected by increased dosage.

Lungs of dying or dead rats were congested.

Conclusions:

LC_{50} Males = 2.27 mg/l; Females = 3.52 mg/l

Toxicity Category: IV based on LD_{50} > 2.0 mg/l

CORE Classification: Guideline

DATA EVALUATION RECORD FOR PRIMARY EYE IRRITATION TESTING §81-4

Product Manager (PM): 31 EPA Reg. No.: 67071-R

Reviewer: David L. Ritter, Toxicologist DLR 10-19-94

MRID No.:427465-14

Testing Laboratory: Huntingdon Research Centre Ltd.,
PO Box 2, Huntingdon
Cambridgeshire PE18 6ES England

Title Of Report: Eye Irritation to the Rabbit of Acticide LG

Date of Report: 8/8/91

Lab. No.: 9127D/THR 14/SE

Author(s): M. P. Liggett & Lewis A. McRae

Species: New Zealand white rabbit

Sex: F Wt.: 3.7 kg

Source: Froxfield Farms, Petersfield, Hampshire

Test Material: Acticide LG undiluted

Dosage: 0.1 ml in lower eyelid.

Quality Assurance (40 CFR 160.12): Acceptable

Summary:

Procedure (note any serious deviation from §81-4):

Standard laboratory animal husbandry and GLP were followed.

Animal was weighed initially and at termination.

Animal was examined for corneal damage prior to instillation of Test Article.

Test Article Administration:

Test Article was administered by everting the lower eyelid and instilling 0.1 ml Test Article.

Eye were examined using the Draize scoring system for eye irritation at 1 hour and on days 1, 2 and 3.

/2

Results:

Study was terminated after 3 days because of severity of irritation (+2 for corneal involvement and +3 for conjunctival involvement).

Animal showed corneal opacity and iridial inflammation that was still present after three days.

Conclusions:

TOX Category: I based on severe corneal, iridial and conjunctival irritation at three days in a single animal.

CORE Classification: Guideline.

13

DATA EVALUATION RECORD PRIMARY DERMAL IRRITATION TESTING§81-5

Product Manager (PM): 31 EPA Reg. No.: 67071-R

Reviewer: David L. Ritter, Toxicologist DLR 10-19-94

MRID No.:427465-15

Testing Laboratory: Huntingdon Research Centre Ltd.,
PO Box 2, Huntingdon
Cambridgeshire PE18 6ES England

Title Of Report: Skin Irritation to the Rabbit of Acticide LG

Date of Report: 10/30/91

Lab. No.: 9126D/THR 13/SE

Author(s): Michael Liggett & Lewis McCrae

Species: New Zealand white rabbits

Wt.: 2.3 - 3.2 kg

Source: Froxfield Farms Ltd., Petersfield, Hampshire

Test Material: Acticide LG

Dosage: 0.5 ml applied topically

Quality Assurance (40 CFR, Section 160.12): Acceptable

Summary: TOX Category: Not Determined. Classification: Suppl.

Procedure (note any serious deviation from §81-5):

Standard laboratory animal husbandry and GLP were followed.

Animals were clipped free of dorsal hair 24 hours prior to application. 0.5 ml Test Article was applied topically under a gauze patch to an area of approximately 2.5 cm^2. The test sites were then secured with semi-occlusive dressings.

After 4 hours the dressings were removed and the test sites cleansed with water.

Test sites were evaluated for irritation after the method of Draize (1959) at 30 minutes, and at 24, 48 and 72 hours, and on days 5 to 14 following removal of dressings.

14

Results:

DERMAL IRRITATION SCOREBOARD

#Rab	Eschar/Erythema						Edema						Score
	Observation times in hours/days*												
	0.5	2	3	4	7	14	0.5	2	3	4	7	14	
49F	2	2	2	2	1	1	2	2	1	1	1	0	3.5
50F	2	2	2	2	1	0	2	2	1	1	0	0	3.5
51F	2	2	2	2	1	0	3	3	2	2	0	0	4.5
52F	2	2	2	2	2	0	3	2	1	1	1	0	3.5
53F	3	2	2	2	2	1	3	2	2	2	1	0	4.5
54F	2	2	2	2	2	2	3	2	2	2	2	2	4.25

*Observations for days 5 and 6, and days 8 - 13 not included in this table.

Score = sum of numerical grades/no. observation periods at 1, 24, 48 and 72 hours.

PII = Sum of scores/No. animals = 23.75/6 = 3.96

Slight < 2.0; Moderate 2 - 5; Severe > 5

Conclusions:

This product is TOX Category undetermined; study classified Supplementary.

The study is rated CORE Supplementary - irritation persisted beyond day 14; requires observation through day 21.

15

DATA EVALUATION RECORD FOR DERMAL SENSITIZATION TESTING §81-6

Product Manager (PM): 31 EPA Reg. No.: 67071-R

Reviewer: David L. Ritter, Toxicologist DLR 10-19-94

MRID No.:427465-16

Testing Laboratory: Huntingdon Research Centre Ltd.,
PO Box 2, Huntingdon
Cambridgeshire PE18 6ES England

Title Of Report: Skin Sensitization in the Guinea Pig of Acticide LG

Date of Report: 5/15/91

Lab. No.: 91120D/THR 15/SS

Author(s): Brenda Parcell & Guy Healing

Species: Duncan Hartley guinea pig Sex: Female 20/group

Source: D. Hall, Newchurch, Staffordshire, England

Test Material: Acticide LG

Quality Assurance (40 CFR, Section 160.12): Acceptable

Summary:

The data support a conclusion that the product is a dermal sensitizing agent.

CORE Classification: Guideline

Procedure (Deviation From §81-6: (Guinea Pig Maximization Test of Magnusson & Kligman*)

Standard laboratory animal husbandry and GLP were observed.

Animals were observed daily for general physical appearance.

20F for the control group; 20F for the treated group.

Animals were weighed initially and at termination.

Dose levels were selected from a preliminary study.

---

* Magnusson, B. and A.M. Kligman. J. Invest. Dermatol. 52:268-276, 1969.

16

Induction Phase:

Injections

An area of approximately 4 x 6 cm over the shoulder was clipped free of fur. 2 - 0.1 ml intradermal injections were given, one on each side of the midline. The animals received:

Freund's Complete Adjuvant (FCA) diluted 1:1 with water for irrigation (WI).

Test Article 0.25% in WI;

Test Article 0.25% in a 50:50 mixture of FCA in WI.

Control animals were treated similarly but did not receive Test Article.

Topical Applications

Area was re-clipped after one week and a 2 x 4 cm patch of filter paper was saturated with 0.4 ml Test Article 20% in distilled water (DW) was applied to the skin and covered with impermeable dressings for 48 hours.

Challenge Phase:

After two weeks the animals were again clipped and a 2 x 2 cm patch of Whatman 3MM filter paper containing either Test Article 7.5 % or 4.0% in DW was then applied to new sites, an anterior site for the 7.5% and a posterior site for the 4.0%. Application sites were dressed as before and dressings were removed after 24 hours. The test sites were scored for erythema and edema using a scale similar to that of Draize at 24, 48 and 72 hours.

Results:

There were no deaths and no deleterious effects on weight gain.

Induction: (injection)

Necrosis was produced in control and Test animals receiving FCA.

Slight necrosis was seen in Test animals receiving Test Article 0.25% in WI.

No irritation was reported in animals receiving WI only.

Induction: (topical)

Moderate erythema was reported in Test animals receiving Test Article 20% in DW.

Challenge:

Dermal irritation was moderate to severe in all Test animals at 24, 48 and 72 hours. Animals receiving Test Article 7.5 % in DW showed the severest response.

Historical Control Data:

This report included data from historical studies using formalin as the positive control agent. The studies demonstrate that the test system will detect dermal sensitizing agents.

Conclusion(s):

The data support a conclusion that the product is a dermal sensitizing agent.

CORE Classification: Guideline

18

ACUTE TOX ONE-LINER

1. PC CODE: 107103; 5-chloro-2-methyl-3(2H)-isothiazolone

2. CURRENT DATE: 10/17/94

3. TEST MATERIAL: Acticide LG

4. EPA Reg. #: 67071-R

Study/Species/Lab/ Study#/Date	MRID No.	Results	Tox. Cat.	Core Grade
Acute Oral/Rat/HRC*/ 9181D/THR 11/AC/ 5-8-91	427465-11	LD_{50} M = 5.7 mg/kg LD_{50} F = 5.2 mg/kg	IV	G
Acute Dermal/Rat/HRC/ 9182D/THR 12/AC/ 5-8-91	" -12	LD_{50} M&F Limit test = 2000 mg/kg	III	G
Acute Inhal./Rat/ HRC/THR 10/911109/ 4-24-94	" -13	LC_{50} M = 2.3 mg/l LC_{50} F = 3.5 mg/l	IV	G
Acute Eye Irr./ Rabbit/HRC/9127D/THR /8-8-91	" -14	Severe corneal/ conjunctival injury in 1 rabbit. terminated after 3 days.	I	G
Primary Dermal Irr./ Rabbit/HRC/ 9126D/THR 13 SE/ 10-30-91	" -15	Study only followed for 14 days; still had +2 edema; rated supplementary	---	S
Dermal Sens./Guinea pig/HRC/91120D/THR 15/SS/5-15-91	" -16	GMPT sensitizing agent	---	G

*Huntingdon Research Centre Ltd.,
PO Box 2, Huntingdon
Cambridgeshire PE18 6ES England

DOR 10-19-92

Core Grade Key:

G = Guideline
M = Minimum
S = Supplementary